PTO/SB/33 (07-05)

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
020130-000111US

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on April 21, 2006

Signature Malinda C Dagit

Typed or printed name Malinda C. Dagit

Application Number	Filed
09/870,353	May 30, 2001

First Named Inventor
WANG, Yan

Art Unit	Examiner
1652	Richard G. Hutson

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 44,879.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____

Signature

Jean M. Lockyer Reg. No. 44,879
Typed or printed name

415-576-0200
Telephone number

April 21, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

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On 21 April 2006

TOWNSEND and TOWNSEND and CREW LLP

By: [signature]

PATENT
Attorney Docket No.: 020130-000111US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 8319
WANG et al.	Examiner: Richard Hutson
Application No.: 09/870,353	Technology Center/Art Unit: 1652
Filed: May 30, 2001	APPLICANTS' ARGUMENTS FOR PRE-APPEAL BRIEF REVIEW - EXAMINING GROUP 1652
For: IMPROVED NUCLEIC ACID MODIFYING ENZYMES	
Customer No.: 20350	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Final Office Action mailed October 28, 2005, on the above-referenced application, please consider the following arguments. Also filed herewith are a Notice of Appeal, a Request for Pre-Appeal Brief Review, and a Petition with fee authorization for a three-month extension of time.

The invention

The pending claims relate to polymerase proteins that are defined by two domains. The first domain is a polymerase domain. The second domain is a nucleic acid binding domain that improves the processivity of the polymerase. The nucleic acid binding domain is characterized by its percent identity to a prototype protein, Sso7d or Sac7d.

Rejection under 35 U.S.C. § 112, first paragraph-enablement

In the Final Office Action of October 28, 2005, claims 15, 17, 20, 22-30, and 32-42 are rejected under 35 U.S.C. §112 for alleged lack of enablement. The Examiner's position is that it would require undue experimentation to determine Sso7d and Sac7d variants having DNA binding properties and 75%-85% identity to the reference Sso7d and Sac7d sequences set forth in the claims. In brief, the Examiner argues that the specification fails to establish: i) regions of the nucleic acid binding domain that can be modified without affecting binding activity; ii) the general tolerance of the domain for modification, and iii) a predictable scheme for modifying amino acid residues of the domain with an expectation of obtaining the desired biological function.

Applicants' arguments

Applicants have fully rebutted this rejection during prosecution. The specification provides examples that show that both Sso7d and Sac7d increase processivity when joined to polymerases (*see, e.g.,* the Examples section), and directs the practitioner to the large body of art in this field that provides detailed structural insight into the interaction of Sso7d and Sac 7d with DNA. In addition, a Declaration under 37 C.F.R. § 1.132 by Dr. Peter Vander Horn (submitted with Applicants' response filed November 17, 2004 and referred to herein as "the Vander Horn Declaration") provides objective reasons justifying the percent identity recited in the current claims.

State of the art at the time of the invention

The nucleic acid binding domain set forth in the claims is not derived from a novel gene. It is an old family of 18 known members. A natural variation of about 76% occurs within the family (as noted in the Vander Horn Declaration, which is discussed in greater detail below). Analyses of the structures of Sso7d and Sac7d bound to DNA have been performed by several investigators. The specification in fact directs a practitioner to exemplary references describing such studies *(e.g.*, Baumann *et al. Structural Biol* 1:808-819, 1994 and Gao *et al., Nature Struc. Biol* 5:782-786, 1998; both cited in paragraph 44; copies provided as Exhibits 9

and 3, respectively, of the Vander Horn Declaration). Baumann *et al.* teach NMR structural analysis of the DNA binding surface of Sso7d. Gao *et al.* teach Sso7d-DNA structures determined using x-ray crystallography.

Similar x-ray crystallographic analysis has also been performed for the related protein Sac7d (*e.g.*, Robinson, *et al., Nature* 392:202-205, 1998, which reference is cited in Gao *et al.*). Gao *et al.* additionally compare the Sso7d-DNA complex to Sac7d-DNA complex. Thus, at the time of the invention, those of skill in the art had extensive information available to them regarding regions and specific residues of Sso7d that are involved in the binding interaction of the protein with DNA. Accordingly, the disclosure in the application, when filed, contains sufficient information to enable one of skill in the art to make and use the invention.

Applicants have provided objective reasons justifying the percent identity set forth in the claims

Not only does the subject specification provide a full disclsoure of the family of Sso7 proteins, Applicants have provided the Vander Horn declaration, which provides objective reasons justifying the 75% identity level. Dr. Vander Horn explains that by following the differences between the family members, those of skill would immediately recognize where the critical and noncritical regions of the proteins are located. The family members are a virtual roadmap to novel variants. Dr. Vander Horn additionally explains how the prior art, *e.g.*, Gao *et al.*, provide structure-activity relationships that can be used in determining residues that can be substituted without compromising activity.

According to Dr. Vander Horn, a GenBank search of Sso7d readily identifies at least 18 known DNA binding proteins that have amino acid identities of between 98-79%. In another search, he identified an endonuclease from the Archeon *Methanococcus jannashi*i with a subsequence with a 47% identity to Sso7d. Clearly, this group of proteins represents an old family tree. The natural genetic drift is a guide to novel muteins. As Dr. Vander Horn explains in the Declaration, to limit the claims to a percentage above that found within the naturally occurring variants is to ignore that nature has provided this road map to muteins. Indeed, in section 13 of his declaration, Dr. Vander Horn has created a hybrid protein combining known natural variations to obtain a protein with 76% identity to Sso7d.

In addition to the natural variations between family members, any competent protein chemist readily understands that non-naturally occurring but conserved substitutions are possible throughout the primary sequences of the prototype proteins. Dr. Vander Horn explains this conventional wisdom at section 9 of his Declaration.

Last, Dr. Vander Horn explains at section 10 of his Declaration that the SAR of the Archeal protein interaction with DNA had been previously studied by workers such as Gao *et al.* Dr Vander Horn details how this information permits a practitioner to identify the critical binding domains in the proteins, which allows one of skill to focus mutations away from these critical regions.

The Vander Horn Declaration thus illustrates how one of skill in the art can use the large body of knowledge in the art to identify functional Sso7d variants having the percent identity set forth in the claims without undue experimentation.

Recent Board decision supports allowing the claims

Applicants request that the Examiner take note of the Board's recent decision in *Ex parte Yuejin Sun et. al.* Although, the *Sun* case was unpublished, the facts are so similar to Applicants' circumstances that the opinion is powerfully persuasive in favor of allowing the pending claims. A copy of the decision was provided with Applicants' response filed November 17, 2004.

In *Sun*, the invention was a novel plant gene encoding a protein called 'wee1'. The claims at issue claimed a nucleic acid having "at least 80% identity to the entire coding region of SEQ ID No: 1." The examiner had applied both a description and enablement rejection. The Board of Appeals reversed both the description and enablement rejections.

To support the enablement rejection, the examiner in *Sun* employed the same arguments presented in the Final Office Action. Those arguments were: (i) there was no structure activity relationship; (ii) there were no predictable means taught for modifying the prototype coding region to 80% identity while retaining activity; and, (iii) there were insufficient examples. Although not cited by name, the Board reversed the rejections applying the principle set forth in *In re Angstadt and Griffen*, 190 USPQ 214 (CCPA 1976). In *Angstad*,

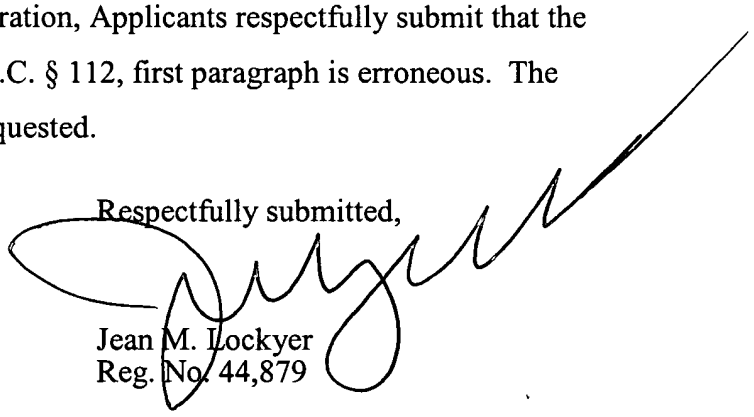
the CCPA ruled that claims that embraced some non-working embodiments were permitted under §112 so long as a functional assay was provided that allowed those of skill to routinely avoid non-working embodiments. In *Sun*, the Board recognized that the appealed claim was enabled by the disclosure of a functional assay to routinely determine when you had proteins that functioned and by the fact that modifications to the primary amino acid sequence of wee 1 were also routine.

In comparison to *Sun*, the facts of the instant case are even more compelling towards claim allowance. In *Sun*, the gene was novel and was the invention per se. In the instant application, the recited gene family is a mere claim element and is both a well known and well characterized family. Applicants have provided objective evidence that the claim limitation of 75% to 85% identity to Sso7d is a reasonable approximation of the ability of protein chemists to alter the primary sequence of the prototype while maintaining biological function.

Conclusion

In view of the teachings in the specification, the advanced state of the art, and the evidence provided in the Vander Horn Declaration, Applicants respectfully submit that the rejection of the pending claims under 35 U.S.C. § 112, first paragraph is erroneous. The withdrawal of the rejection is respectfully requested.

Respectfully submitted,



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